40. The method of claim 14 wherein the oligonucleotide comprises SEQ ID NO: 31.

REMARKS

Claims 1-33 are pending in the instant application. Claims 1-33 have been rejected. Claims 1-13, 15-20 and 23-27 have been canceled. Claims 14, 21, 22 and 28 have been amended. New claims 34-40 have been added to incorporate subject matter from the canceled claims with respect to the methods of the instant invention. No new matter has been added by these additions or amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Specification

The Examiner suggests that correction of the address for the American Type Culture Collection is needed. Applicants have amended the specification as requested at pages 64 and 102 to provide the correct address.

II. Double-Patenting

Claims 1-25 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of U.S. Patent No. 6,221,850, claims 1 and 2 of U.S. Patent No. 5,877,309, and claims 1-3 of U.S. Patent No. 6,133,246. The Examiner suggests that although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-13, 15-20 and 23-25 have been canceled making this rejection as it pertains to those claims moot. With respect to claims 14, 21 and 22, a terminal disclaimer has been filed herewith as required under 37 CFR 3.73(b). Withdrawal of this rejection is therefore respectfully requested.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1-33 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner suggests that the specification broadly claims oligonucleotides that hybridize with JNK protein but that the applicant has not made clear the genus of the claimed compounds.

In an earnest effort to advance the prosecution of this case, Applicants have canceled claims 1-13, 15-20 and 23-27 and amended the remaining claims (14, 21, 22 and 28-33) to refer to methods of using antisense compounds that are targeted to human JNK2. Support for these amendments can be found throughout the specification as filed but in particular at pages 82-92, 102-103, and 117-126. Accordingly, the claims as amended now recite a specific genus of JNK protein, namely human JNK2.

With respect to the Examiner's comments regarding antisense compounds that are 8-nucleobases in length, by limiting the genus of JNK proteins to human JNK2, the specification as filed provides one of skill with specific guidance on the way to design such small antisense compounds when it now limits the claims to antisense targeted to human JNK2. Further, nowhere in the articles cited by the Examiner (Branch et al., Crooke, and a press release) does it state that antisense compounds at least 8 nucleobases in length that are designed to a specific target (human JNK2 in this case) would be unpredictable in their ability to inhibit gene expression.

As a result of these amendments to the claims, the cancellation of certain claims, and the arguments presented above, withdrawal of this rejection is respectfully requested.

Claims 13-17 and 21-33 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for modulating expression of a JNK protein in cells *in vitro* does not reasonably provide enablement for *in vivo* modulation of JNK expression; the Examiner cites an article on the technology of antisense to support this position. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that the cited reference supports the position that application of antisense *in vivo* is highly unpredictable.

The Examiner has pointed to an article on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads this paper as a whole, as required under MPEP 2141.02, this reference actually teaches the potential usefulness of this class of drugs in humans, and more importantly fails to provide any reasonable basis to doubt the pharmacological activity observed in cells or in animals would also occur in humans. Further, contrary to the Examiner's

suggestion, the specification as filed provides *in vivo* animal data showing the pharmacological activity, *in vivo*, of antisense compounds of the instant invention, including ones targeted to human JNK2 (see pages 102-103).

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological activity in animals and humans. It is a fundamental principle of drug development that

data from whole cell studies, such as are provided in the instant specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [in vitro]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans. Nowhere in the reference does the author state or suggest that results of well-designed *in vitro*

pharmacological studies would not be predictive of activity *in vivo*.

Moreover, the fact that animal data using antisense compounds of the instant invention are also provided in the specification as filed lends further support to the assertion that the specification as filed provides one of skill with the teachings necessary to develop methods for treatment of animals, including humans. Accordingly, withdrawal of the rejection is requested.

IV. Rejection of Claims Under 35 U.S.C. 102(b)

Claims 1, 9, 14 and 20 have been rejected under 35 U.S.C. 102(b) as being anticipated by Seimiya et al. (1997). The Examiner suggests that this paper discloses a 24 mer antisense oligonucleotide specific for the JNK sense sequence of a mammal and its use in cells to modulate expression of JNK.

Applicants are providing herewith a Rule 131 Declaration, which was filed in the parent case (Patent 5,877,309) to overcome the § 102 rejection, evidencing that the paper by Seimiya et al. was published subsequent to the instant invention of antisense oligonucleotides targeted to JNK. Therefore, the paper of Seimiya et al. is not a valid prior art reference under 35 U.S.C. 102(b). It is respectfully requested that this rejection be withdrawn.

Claims 13 and 28-33 have been rejected under 35 U.S.C. 102(b) as being anticipated by Karin et al. (US Patent 5,837,244). The Examiner suggests that this patent discloses a method of treating a cell proliferative disorder associated with JNK by administering a therapeutically effective amount of a reagent, that is an antisense oligonucleotide, that modulates JNK. Applicants respectfully traverse this rejection.

Karin et al. discloses protein kinases, JNK1 and JNK2. JNK1 is characterized by having a molecular weight of 46 kD as determined by SDS-PAGE, serine and threonine kinase activity, and the ability to phosphorylate the c-Jun N-terminal activation. JNK2 is characterized by having a molecular weight of 55 kD and activity similar to JNK1. This reference also teaches polynucleotides which encode the JNK polypeptide and a synthetic peptide which binds to the c-Jun N-terminal kinase, JNK. However, nowhere in this reference are any antisense oligonucleotide sequences that are complementary to the sequence of human JNK2 specifically taught and as now claimed. Nor does this reference provide any teaching of particular antisense compounds or antisense sequences, as taught in the specification as filed. Accordingly, this general teaching of the possibility of developing antisense agents against JNK2 also fails to provide any reasonable expectation of success or teachings

or suggestion which render obvious antisense oligonucleotides targeted to a nucleic acid encoding human JNK2 protein or uses of these specific antisense oligonucleotides which inhibit expression of human JNK2 protein to treat conditions or diseases in animals. Accordingly, this reference fails to teach the limitations of the claims as amended, which recite methods based on use of antisense compounds targeted to human JNK2, and cannot anticipate the instant invention (MPEP 2131). Withdrawal of this rejection is respectfully requested.

V. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1-33 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Seimiya et al., Baracchini et al. (US Patent 5,801,154), Shibahara et al. (1989), Kallunki et al. (1994), and Karin et al. (US Patent 5,837,244). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill to make the antisense of claim 1 as taught by Seimiya et al., with the modifications as taught by Baracchini et al. and Shibahara et al., with different sequences as taught by Kallunki et al. The Examiner further suggests one of skill would have been motivated by the combined teachings and also have had an expectation of success. Applicants respectfully traverse this rejection.

At the outset, and as discussed *supra*, claims 1-13, 15-20 and 23-27 have been canceled. Claims 14, 21, 22 and 28-33 have been amended to recite that the methods of the instant invention are based on use of antisense compounds targeted to human JNK2.

Also as discussed *supra*, the reference of Seimiya et al. was published after the priority date of the instant invention and is thus not a valid prior art reference under 35 U.S.C. 103(a).

Baracchini et al. (US Patent 5,801,154) disclose antisense compounds targeted to multidrug resistance associated protein and uses thereof. Although modification of antisense compounds is taught, nowhere does this patent teach or suggest methods for using antisense compounds targeted to human JNK2.

Shibahara et al. (1989) teach oligonucleotides for use to inhibit HIV and ways to modify oligonucleotides. This reference, however, does not teach or suggest antisense oligonucleotides against JNK of any species, including human JNK2 as claimed, and their uses as claimed. Nor is there any suggestion to target the JNK gene with antisense agents. Accordingly, this reference provides no reasonable expectation that antisense agents targeted to JNK would be successful nor does it teach or suggest the gene to be targeted by antisense agents or any specific antisense oligonucleotides.

Kallunki et al. (1994) teach that a nucleic acid encoding a first isoform of a JNK protein is not identical to the second isoform. This reference, however, does not teach or suggest antisense oligonucleotides against JNK of any species. Nor is there any suggestion to target the JNK gene with antisense agents. Accordingly, this reference provides no reasonable expectation that antisense agents targeted to JNK would be successfully used as now claimed.

As discussed *supra*, Karin et al. disclose the protein kinases, JNK1 and JNK2. JNK1 is characterized by having a molecular weight of 46 kD as determined by SDS-PAGE, serine and threonine kinase activity, and the ability to phosphorylate the c-Jun N-terminal activation. JNK2 is characterized by having a molecular weight of 55 kD and activity similar to JNK1. This reference also teaches polynucleotides which encode the JNK polypeptide and a synthetic peptide which binds to the c-Jun N-terminal kinase, JNK. However, nowhere in this reference are any antisense oligonucleotide sequences that are complementary to the sequence of human JNK2 specifically taught as now claimed. Nor does this reference provide any teaching of particular antisense compounds or antisense sequences, as taught in the specification as filed. Accordingly, this general teaching of the possibility of developing antisense

agents against JNK2 also fails to provide any reasonable expectation of success or teachings or suggestion which render obvious antisense oligonucleotides targeted to a nucleic acid encoding human JNK2 protein or uses of these specific antisense oligonucleotides which inhibit expression of human JNK2 protein.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Seimiya et al. is not a valid reference under 103(a). This fact combined with the lack of teaching of the other references when combined of successful use of human JNK2 targeted antisense as claimed is clear evidence for the lack of obviousness of the instant invention. Thus, the combination of prior art cited fails to teach or suggest the limitations of the claims as amended, as well as failing to provide for an expectation of success for the claimed methods. Therefore, this combination of cited art cannot render the instant claimed invention obvious. Withdrawal of this rejection is therefore respectfully requested.

Claims 1, 14, 16 and 18 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Derijard et al. (1994), in view of Karin et al. (WO 95/03324) and Milligan et al. (1993). The Examiner suggests that it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to make 15 mer antisense oligonucleotides targeted to a JNK encoding nucleic acid that modulated expression of a JNK protein as suggested by Karin using the JNK sequence of Derijard et al. The Examiner suggests that motivation is provided by the teaching of Karin et al., while Milligan provide for the expectation of success in teaching that antisense may be designed for genes whose sequence is known. Applicants respectfully traverse this rejection.

As discussed *supra*, claims 1, 16 and 18 have been canceled making this rejection as it pertains to those claims moot. Claim 14 has been amended to recite that the JNK nucleic acid molecule used to inhibit expression of JNK2 protein in cells or tissues is a human JNK2 nucleic acid molecule.

Derijard et al. merely disclose a nucleotide sequence of a cDNA encoding JNK protein. As acknowledged by the Examiner, this primary reference does not teach antisense oligonucleotides against JNK, or uses of such compounds. Nor is there any suggestion in this reference to target the JNK gene with antisense agents.

Accordingly, this reference provides no reasonable expectation that antisense agents targeted to JNK would be successful nor does it teach or suggest any specific antisense oligonucleotides or their uses as claimed.

The secondary references cited by the Examiner, namely Karin et al. and Milligan et al., fail to remedy the deficiencies of the primary teaching by Derijard.

Karin et al. disclose protein kinases, JNK1 and JNK2. JNK1 is characterized by having a molecular weight of 46 kD as determined by SDS-PAGE, serine and threonine kinase activity, and the ability to phosphorylate the c-Jun N-terminal activation. JNK2 is characterized by having a molecular weight of 55 kD and activity similar to JNK1. This reference also teaches polynucleotides which encode the JNK polypeptide and a synthetic peptide which binds to the c-Jun N-terminal kinase, JNK. At page 16, beginning at line 16, Karin et al. teach that "the polynucleotide sequence for JNK also includes sequences complementary to the polynucleotide encoding JNK (antisense sequences)" and suggest that "the invention embraces all antisense polynucleotides capable of inhibiting production of JNK polypeptides." However, nowhere in this reference are any antisense oligonucleotide sequences specifically taught. Accordingly, this general teaching of the possibility of

developing antisense agents against human JNK2 also fails to provide any reasonable expectation of success or teaching or suggestion which render obvious antisense oligonucleotides targeted to a nucleic acid encoding human JNK2 protein or uses of these specific antisense oligonucleotides to inhibit expression of human JNK2 protein.

Milligan et al. provides no teaching whatsoever with respect to antisense agents against JNK but rather is a general review article summarizing concepts as of 1993 in antisense drug design.

Accordingly, this combination of prior art references fails to provide any reasonable expectation of success or a suggestion or teaching which render obvious antisense oligonucleotides targeted to human JNK2 of the instant invention. Accordingly, these references when combined cannot establish a *prima facie* case of obviousness (MPEP 2143) and withdrawal of this rejection is respectfully requested.

Claims 2-9 and 19 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Derijard et al., Karin et al., and Milligan et al., as taken together and applied to claims 1, 14, 16 and 18 above, and further in view of Shibahara et al. and Kallunki et al. Applicants have canceled claims 2-9 and 19. Therefore, withdrawal of this rejection is respectfully requested.

Attorney Docket No.: **ISPH-0526**
Inventors: **McKay et al.**
Serial No.: **09/774,809**
Filing Date: **January 31, 2001**
Page 21

VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **January 3, 2003**

LICATA & TYRRELL P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at page 64, line 12, has been amended as follows:

-In order to evaluate the activity of potential JNK-modulating oligonucleotides, human lung carcinoma cell line A549 (American Type Culture Collection, ~~Rockville, MD~~ 10801 University Boulevard, Manassas, VA 20110-2209, No. ATCC CCL-185) cells or other cell lines as indicated in the Examples, were grown and treated with oligonucleotides or control solutions as detailed below. After harvesting, cellular extracts were prepared and examined for specific *JNK* mRNA levels or JNK protein levels (*i.e.*, Northern or Western assays, respectively). In all cases, "% expression" refers to the amount of JNK-specific signal in an oligonucleotide-treated cell relative to an untreated cell (or a cell treated with a control solution that lacks oligonucleotide), and "% inhibition" is calculated as

100% - %Expression = %Inhibition.--

Paragraph beginning at page 102, line 3, has been amended as follows:

-Approximately 5 x 10^6 breast adenocarcinoma cells (cell line MDA-MB-231; American Type Culture Collection, ~~Richmond, VA~~ 10801 University Boulevard, Manassas, VA 20110-2209, No. ATCC HTB-26) were implanted subcutaneously in the right inner thigh of nude mice (n=6 for each of three sets of mice). Oligonucleotides ISIS 15346 (JNK1, SEQ ID NO:16) and 15353 (JNK2, SEQ ID NO:31) were suspended in saline and administered once daily to two sets of mice on the first day the tumor volume was about 100 mm^3. A saline-only (0.9% NaCl) solution was given to a third set of animals as a control. Oligonucleotides were given by intravenous injection at a dosage of 25 mg/kg. Tumor size was measured and tumor volume was calculated on days 12, 19, 26 and 33 following tumor cell inoculation.--

In the Claims:

Please cancel claims 1-13, 15-20 and 23-27 without prejudice.

Please amend the claims as follows:

14. (amended) A method of modulating the expression of ~~a~~ human JNK2 protein in cells or tissues comprising contacting said cells or tissues with ~~the~~ an oligonucleotide ~~of claim 1~~ from 8 to

30 nucleotides connected by covalent linkages, and wherein said oligonucleotide has a sequence specifically hybridizable with a nucleic acid molecule encoding human JNK2 protein and said oligonucleotide modulates the expression of said human JNK2 protein.

21. (amended) A method of inhibiting the growth of a tumor in an animal comprising administering to said animal an effective amount of ~~the~~ a pharmaceutical composition ~~of claim 10~~ comprising an oligonucleotide from 8 to 30 nucleotides connected by covalent linkages and a pharmaceutically acceptable carrier, and wherein said oligonucleotide has a sequence specifically hybridizable with a nucleic acid molecule encoding human JNK2 protein and said oligonucleotide inhibits growth of said tumor in said animal.

22. (amended) ~~A~~ The method of claim 21 ~~inhibiting the growth of a tumor in an animal~~ wherein said pharmaceutical composition further comprisinges ~~administering to said animal an effective amount of the pharmaceutical composition of claim 11~~ one or more compounds, wherein said compounds include a stabilizing agent, a penetration enhancer, and a chemotherapeutic agent.

28. (amended) A method of treating an animal having a disease or condition associated with a human JNK2 protein comprising administering to said animal a therapeutically or prophylactically effective amount of ~~the compound of claim 1~~ an oligonucleotide from 8 to 30 nucleotides connected by covalent linkages and a pharmaceutically acceptable carrier, wherein said oligonucleotide has a sequence specifically hybridizable with a nucleic acid molecule encoding human JNK2 protein, so that expression of the human JNK2 protein is inhibited.